Ganciclovir

Brand Name: Cytovene, Cytovene-IV (sodium salt), Vitrasert

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Drug Description

Ganciclovir is a synthetic purine nucleoside analogue of guanine. It is structurally and pharmacologically similar to acyclovir, but it has increased antiviral activity against CMV and decreased selectivity for viral DNA. [1]

HIV/AIDS-Related Uses

Ganciclovir was approved by the FDA on June 23, 1989. Parenteral ganciclovir is approved by the FDA for induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Oral ganciclovir is approved for maintenance treatment of CMV retinitis in patients whose active retinitis was resolved by IV induction therapy. Oral ganciclovir is also approved for the prophylaxis of CMV disease in patients with advanced HIV infection who are at risk for developing CMV disease. [2] [3] FDA Approved Drugs for HIV/AIDS] Off-label uses of parenteral ganciclovir include the treatment of severe cytomegalovirus disease, including CMV pneumonia, CMV gastrointestinal disease, CMV radiculopathy, and disseminated CMV infections in patients with AIDS and other immunocompromised patients. [4]

Ganciclovir intravitreal implant was approved by the FDA on March 5, 1996 for the intraocular treatment of cytomegalovirus retinitis in patients with AIDS. [5]

Non-HIV/AIDS-Related Uses

Parenteral ganciclovir is approved for treatment of CMV retinitis in immunocompromised patients. Oral ganciclovir is approved for maintenance treatment of CMV retinitis in immunocompromised patients who have stable retinitis after intravenous induction therapy and for the prevention of CMV disease in transplant patients who are at risk for the disease. [6] [7]

Pharmacology

Ganciclovir is a prodrug that is transformed into ganciclovir triphosphate by cellular kinases. The active phosphorylated form of ganciclovir inhibits replication of CMV and other human herpesviruses by interfering with DNA synthesis by competing with deoxyguanosine for incorporation into viral DNA and by terminating DNA synthesis at the point of incorporation. [8] Concentrations of ganciclovir triphosphate may be as much as 100-fold greater in CMV-infected than in uninfected cells, indicating preferential phosphorylation in infected cells. Ganciclovir triphosphate, once formed, persists for days in the CMV-infected cell. [9]

Ganciclovir is absorbed poorly from the gastrointestinal tract. Under fasting conditions, the absolute bioavailability of oral ganciclovir is about 5% and, when administered with food, 6% to 9%. In HIV infected individuals receiving 1 g of oral ganciclovir every 8 hours with food, the steady-state area under the concentration-time curve (AUC) increased by about 22%, peak serum concentrations (Cmax) increased from 0.85 to 0.96 mcg/ml, and the time to peak concentration increased from 1.8 to 3 hours as compared to fasting administration. [10]

Although the distribution of ganciclovir into human tissue and fluid is not fully understood, autopsy findings show that IV-administered ganciclovir concentrates in the kidneys, with lower concentrations in the lung, liver, brain, and testes. One study in individuals with normal renal function showed that steady-state distribution of the drug averaged 32.8 to 44.5 L/1.73 m2 following IV administration. In individuals with renal impairment, distribution appears to be reduced. Ganciclovir crosses the blood-brain barrier; cerebrospinal fluid concentration of ganciclovir following IV administration averaged 41%. [11]

Limited data show that ganciclovir has good intraocular distribution. Following IV administration, one adult had subretinal concentrations of ganciclovir of 0.87 and 2 times concurrent plasma concentrations at 5.5 and 8 hours, respectively. Concentrations of ganciclovir in the aqueous humor and vitreous humor of another adult were 0.4 and 0.6 higher, respectively, than concurrent plasma concentrations at 2.5 hours

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Pharmacology (cont.)

following IV administration. [12]

Ganciclovir is in FDA Pregnancy Category C. There are no adequate or controlled studies in pregnant women; however, ganciclovir has been shown to be teratogenic in rabbits and embryotoxic in mice. Based on this evidence, ganciclovir may be teratogenic and embryotoxic in humans when given at usual therapeutic dosages. It is not known whether ganciclovir is distributed into milk in humans; however, it is distributed into milk in laboratory animals and causes significant adverse effects in their offspring. [13] [14]

Ganciclovir is 1% to 2% bound to plasma proteins at drug concentrations of 0.5 to 51 mcg/ml. Other than intracellular phosphorylation, ganciclovir is not metabolized appreciably in humans. Serum half-life in individuals with normal renal function is from 2.5 to 3.6 hours following IV administration and from 3.1 to 5.5 following oral administration. In individuals with renal impairment, serum half-life is from 9 to 30 hours following IV administration and from 15.7 to 18.2 hours following oral administration. Approximately 90% to 99% of the drug is excreted unchanged in urine. Renal excretion of ganciclovir occurs mainly via glomerular filtration, although limited tubular secretion may also occur. Doses and frequency of administration of the drug should be modified according to creatinine clearance. Hemodialysis reduces plasma concentrations of ganciclovir by about 50%. [15]

Resistance to ganciclovir is defined as CMV with an in vitro IC50 greater than 3.0 mcg/ml (12.0 microM). Resistance has been observed in patients receiving prolonged IV treatment for CMV retinitis. CMV resistance to ganciclovir has also been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described that contain mutations in the UL97 protein of CMV, which controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir. [16]

The ganciclovir intravitreal implant is designed to release ganciclovir over a period of 5 to 8 months. In one clinical trial, the median time to progression of CMV retinitis after insertion of the implant was 210 days. With the comparison treatment (recommended induction and maintenance doses of intravenous ganciclovir), the median time to progression of CMV retinitis was 120 days. [17]

Adverse Events/Toxicity

The most frequent and clinically significant adverse effects of oral and IV ganciclovir are neutropenia, retinal detachment, and thrombocytopenia. Neutropenia and thrombocytopenia in individuals receiving ganciclovir therapy may be severe and sometimes fatal. AIDS patients may be at greater risk for neutropenia and retinal detachment compared with other immunocompromised patients. [18]

Other adverse effects of oral and IV ganciclovir are abdominal pain, anemia, anorexia, behavioral changes, diarrhea, fever, headache, infection, renal impairment, and vomiting. [19]

In animal studies, ganciclovir was carcinogenic and teratogenic and caused aspermatogenesis. Usual doses of ganciclovir are likely to cause temporary or permanent inhibition of spermatogenesis in men and may suppress fertility in women. [20] Because of ganciclovir's high toxicity and mutagenic and teratogenic potential, use in pregnant women should be avoided. In addition, women of childbearing age should use effective contraception. Men should use barrier contraception during treatment and for at least 90 days following treatment. [21]

Because solutions of ganciclovir are alkaline (pH 11), direct contact of capsule powder or parenteral solution with skin or with mucous membranes can cause irritation or burning. [22]

Adverse effects of intravitreal ganciclovir include bacterial endophthalmitis, conjunctival scarring, foreign body sensation, retinal detachment, scleral induration, and subconjunctival hemorrhage. [23]

Ganciclovir

Drug and Food Interactions

Ganciclovir capsules should be taken with food to increase the drug's bioavailability. [24]

Concurrent administration of ganciclovir with nephrotoxic drugs such as amphotericin B and cyclosporine may increase the risk of renal function impairment, which could subsequently decrease ganciclovir elimination and increase the risk of toxicity. [25]

Drugs with potential for clinically significant interaction with ganciclovir include bone marrow depressants, didanosine, imipenem and cilastin (in combination), probenecid, and zidovudine. [26]

Ganciclovir has exhibited additive or synergistic antiviral activity with foscarnet against CMV and herpes simplex virus type 2 (HSV-2). Combined therapy may be effective in treatment of CMV infection that is resistant to either drug alone. [27]

Contraindications

Ganciclovir is contraindicated in patients with hypersensitivity to ganciclovir or acyclovir. Also, ganciclovir should not be administered if the absolute neutrophil count is less than 500 cells/microL or the platelet count is less than 25,000 cells/microL. [28] Patients with contraindications for intraocular surgery, such as external infection or severe thrombocytopenia, should not receive ganciclovir intravitreal implants. [29]

Because oral ganciclovir is associated with a risk of more rapid rate of CMV retinitis progression, it should be used as maintenance treatment only in those patients for whom this risk is balanced by the benefit of avoiding daily IV infusions. [30]

Clinical Trials

For information on clinical trials that involve Ganciclovir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Ganciclovir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral, intravenous, or intravitreal. [31] [32]

Dosage Form: Ganciclovir capsules containing 250 mg and 500 mg; ganciclovir sodium for injection in 10 ml sterile vials, each containing the equivalent of 500 mg of ganciclovir; intravitreal implant, consisting of a ganciclovir tablet embedded in a nonerodible polymer-based system, delivering a minimum of 4.5 mg of the drug. [33] [34]

Storage: Ganciclovir capsules should be stored at temperatures between 5 and 25 C (41 and 77 F). Ganciclovir sodium vials for injection should be stored at temperatures below 40 C (104 F) and protected from freezing. [35] Ganciclovir intravitreal implants should be stored at temperatures between 15 and 30 C (59 and 86 F) and protected from freezing and from excessive heat and light. [36]

Chemistry

CAS Name: Ganciclovir: 6H-Purin-6-one,2-amino-1,9-dihydro-9-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-[37]

Ganciclovir sodium: 6H-Purin-6-one,1,9-dihydro-2-amino-9-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-, monosodium salt[38]

CAS Number: Ganciclovir: 82410-32-0[39]

Ganciclovir sodium: 107910-75-8[40]

Molecular formula: Ganciclovir: C9-H13-N5-O4; Ganciclovir sodium: C9-H12-N5-NaO4[41]

Ganciclovir: C42.35%, H5.13%, N27.44%, O25.07%; Ganciclovir sodium: C38.99%, H4.36%, N25.26%, O23.09%, Na8.30%[42]

Molecular weight: Ganciclovir: 255.23; Ganciclovir sodium: 277.21[43]

Melting point: 250 C[44]

Physical Description: White to off-white crystalline lyophilized powder. [45]

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Chemistry (cont.)

Stability: After reconstitution, ganciclovir injection solution retains potency for 12 hours at room temperature. Refrigeration is not recommended. After further dilution for intravenous infusion, solutions should be refrigerated and used within 24 hours to reduce the risk of bacterial contamination. [46]

Solubility: Ganciclovir sodium has a solubility of 3 mg/ml in water at 25 C and neutral pH. Ganciclovir and ganciclovir sodium are freely soluble in water at high pH and less soluble at more neutral pH. [47]

Other Names

2'-NDG[48]

2'-Nor-2'-deoxyguanosine[49]

BW-759U[50]

RS-21592[51]

Biolf 62[52]

Cymevan[53]

Cymevene[54]

Ganciclovirum[55]

Gancyclovir[56]

Guanine, 9-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-[57]

Nordeoxyguanosine[58]

RS 21592 Sodium[59]

Further Reading

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Manufacturer Information

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Manufacturer Information (cont.)

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Cytovene
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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